

E1
contd

B. Schneider, N. Thanki, H. Weissig, J. D. Westbrook and C. Zardecki, The Protein Data Bank, Acta Cryst. (2002). D58, 899-907); and BIND (Bader, et al., Nucleic Acids Res 29(1):242-245. (2001)).

Please replace the paragraph found on page 13, beginning at line 21 with the following paragraph.

E2

Similarly, structural alignment of structurally related proteins can be done to generate sequence alignments. There are a wide variety of such structural alignment programs known. See for example VAST from the NCBI (Gibrat, et al., Curr Opin Struct Biol 6(3):377-385. (1996)); SSAP (Orengo and Taylor, Methods Enzymol 266(617-635 (1996)) SARF2 (Alexandrov, Protein Eng 9(9):727-732. (1996)) CE (Shindyalov and Bourne, Protein Eng 11(9):739-747. (1998)); (Orengo et al., Structure 5(8):1093-108 (1997); Dali (Holm et al., Nucleic Acid Res. 26(1):316-9 (1998), all of which are incorporated by reference). These structurally-generated sequence alignments can then be examined to determine the observed sequence variations.

Please replace the paragraph found on page 13, beginning at line 29 with the following paragraph.

E3

Primary libraries can be generated by predicting secondary structure from sequence, and then selecting sequences that are compatible with the predicted secondary structure. There are a number of secondary structure prediction methods, including, but not limited to, threading (Bryant and Altschul, Curr Opin Struct Biol 5(2):236-244. (1995)), Profile 3D (Bowie, et al., Methods Enzymol 266(598-616 (1996); MONSSTER (Skolnick, et al., J Mol Biol 265(2):217-241. (1997); Rosetta (Simons, et al., Proteins 37(S3):171-176 (1999); PSI-BLAST (Altschul and Koonin, Trends Biochem Sci 23(11):444-447. (1998)); Impala (Schaffer, et al., Bioinformatics 15(12):1000-1011. (1999)); HMMER (McClure, et al., Proc Int Conf Intell Syst Mol Biol 4(155-164 (1996)); Clustal W (Higgins D., Thompson J., Gibson T. Thompson J.D., Higgins D.G., Gibson T.J.(1994). CLUSTAL W: improving the sensitivity of progressive multiple sequence alignment through sequence weighting, position-specific gap penalties and weight matrix choice. Nucleic Acids Res. 22:4673-4680); BLAST (Altschul, et al., J Mol Biol 215(3):403-410. (1990)), helix-coil transition theory (Munoz and Serrano, Biopolymers 41:495, 1997), neural networks, local structure alignment and others (e.g., see in Selbig et al., Bioinformatics 15:1039, 1999).

Please replace the paragraph found on page 2, lines 4-6 with the following paragraph.

E4

In particular, U.S.S.N.s 60/061,097, 60/043,464, 60/054,678; PCT US98/07254; and USSN: 09/127,926, now US Patent No. 6,269,312, issued July 31, 2001, describe a method termed "Protein Design Automation", or PDATM, that utilizes a number of scoring functions to evaluate sequence stability.
